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Abstract

Purpose of the review: Chronic lung allograft dysfunction (CLAD) remains a life-threatening complication following lung transplantation. Different CLAD phenotypes have recently been defined, based on the combination of pulmonary function testing and chest CT scanning and spurred renewed interests in differential diagnosis, risk factors and management of CLAD.

Recent findings: Given their crucial importance in the differential diagnosis, we will discuss the latest development in assessing the pulmonary function and chest CT scan, but also their limitations in proper CLAD phenotyping, especially with regards to patients with baseline allograft dysfunction. Since no definitive treatment exists, it remains important to timely identify clinical risk factors, but also to assess the presence of specific patterns or biomarkers in tissue or in broncho alveolar lavage in relation to CLAD (phenotypes). We will provide a comprehensive overview of the latest advances in risk factors and biomarker research in CLAD. Lastly, we will also review novel preventive and curative treatment strategies for CLAD.

Summary: Although this knowledge has significantly advanced the field of lung transplantation, more research is warranted because CLAD remains a life-threatening complication for all lung transplant recipients.

Key words: Chronic lung allograft dysfunction, Bronchiolitis obliterans syndrome, Restrictive allograft syndrome

Introduction

Lung transplantation (LTx) is the ultimate treatment option for selected patients with end-stage pulmonary diseases. Short-and long-term complications limit the overall survival of LTx. The major long-term complication remains chronic lung allograft dysfunction (CLAD). Over the last years, it became clear that different clinical manifestations of CLAD exist leading to the definition of different CLAD phenotypes. Based on the pulmonary function testing and chest CT imaging, a subdivision was proposed in patients with bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed and undefined phenotype (1,2). Importantly, these phenotypes are also associated with different survival trajectories. At present, CLAD is diagnosed by means of spirometry, showing a persistent (at least 3 months) decline in forced expiratory volume in 1 second (FEV_1) with at least 20% compared to baseline, with no other causes of such a decline being present. The baseline FEV_1 is defined as the mean of the two best postoperative FEV_1 measurements, with at least a 3 week interval (1). CLAD can only be diagnosed when there is no other explanation for the decline in FEV_1, such as for instance suture stenosis, development of pleural fluid, myopathy, etc… Moreover, before the definite CLAD diagnosis can be made, a treatment with azithromycin should have been installed for at least 6 weeks, as it is known that azithromycin may restore the decline in FEV_1 to >80% of baseline, in which case the CLAD diagnosis is no longer sustained (2,3).

This spirometric decline in FEV_1 can lead to an obstructive pattern ($FEV_1/FVC<0.7$), which may point to bronchiolitis obliterans syndrome (BOS), or rather a restrictive pattern ($FEV_1/FVC >0.7$), which may allude to restrictive allograft syndrome (RAS) (1,2). To fulfill the criteria for RAS, there should also be persistent opacities on chest CT or X-ray and a concomitant decline in total lung capacity (TLC) of at least 10% compared to the postoperative best value. It is also important to realize that one phenotype can also evolve to the other, which is then called the mixed phenotype (mostly from BOS to RAS) (1,2). Phenotyping of CLAD is important as every phenotype carries a specific prognosis, with RAS having the worst outcome after diagnosis, which was recently also confirmed after living lobar transplantation in Japan (4).

Therefore, this important subdivision has spurred renewed interest in identifying phenotype-specific risk factors and tailored management which we intend to review, specifically focusing on the latest advancements over the last 18 months.

Diagnosis of CLAD

As previously stated, both pulmonary function testing and CT assessment of the transplanted graft are nowadays considered crucial in accurate differential CLAD diagnosis. Consequently, a lot of attention was recently paid to novel modalities to assess the pulmonary function and the chest CT scan.

Although spirometry remains the most important diagnostic tool for CLAD, misinterpretation occurs very often. This is in fact why a lot of authors investigated other possibilities to diagnose CLAD. One of these methods is believed to be impulse oscillometry (IOS), which is highly sensitive to changes in respiratory mechanics. In a recent study in CLAD patients, Crowhurst et al. (5) found a moderate-to-strong correlation between all IOS parameters and spirometry, except resistance at 20 Hz, which is rather a proximal airway measure. They also reported that neither IOS nor spirometry was predictive for the early detection of BOS. In another study including 29 CLAD patients, Vasileva et al. (6) found that intra-subject variability of IOS was independently associated with an increased risk of CLAD, suggesting that further studies on this topic are very much required. In a retrospective, cross-sectional analysis of 263 double lung transplant recipients who underwent paired testing with oscillometry and spirometry, Fu et al. found that different phenotypes of CLAD presented with differences in both spectral and/or intrabreath oscillometry which could prove useful in prognostication (7).

The role of chest CT scan has more recently also been further explored as a possible diagnostic and prognostic tool in CLAD. Habert et al. investigated 118 LTx patients of whom 25 developed CLAD with an initial CT scan and a follow up CT scan at a minimum of 9 months after LTx. They found that moderate pulmonary artery stenosis (30-50%) was associated with the occurrence of CLAD on initial

CT scan and consolidations and pleural effusion on follow up CT scan. In addition, the presence of mosaic attenuation, consolidations and pleural effusions were all risk factors for BOS on follow-up CT scan. The consolidations and pleural effusions were risk factors for death on follow-up CT scan (8). Kubo et al. found that the percentage of low attenuation areas on expiratory CT scan can detect CLAD and especially BOS early (9). CT screening of the donor organ and identifying pulmonary abnormalities in the graft even before the lung transplant was performed, resulted in identifying patterns via machine learning that were indicative of a 19 times increased risk of CLAD development (8). Van Herck et al. demonstrated that the presence and severity of bronchiectasis, and high subscores for mucous plugging, peribronchial thickening or parenchymal involvement are related to worse graft survival. A high score was also associated with a shorter time to BOS onset, lower FEV_1, forced vital capacity, more preceding airway infections, specifically with *Pseudomonas aeruginosa*, and increased airway inflammation (11). In another study, a machine learning tool was used to quantify ground-glass opacity, reticulation, hyperlucent lung and pulmonary vessel volume (PVV) at CLAD diagnosis for phenotyping and prognostication compared with formal radiologist scoring. A total of 88 patients were included, showing that machine learning was able to discriminate between CLAD phenotypes on CT. Both radiologist and machine learning scoring were associated with graft failure, independent of CLAD phenotype. PVV, unique to machine learning, was the strongest in phenotyping and prognostication (12).

In a recent study, exhaled breath analysis using an electronic nose (eNose) seemed to be a promising novel tool for enabling diagnosis and phenotyping CLAD and could therefore be a valuable addition to the diagnostic armamentarium for suspected graft failure in lung transplant recipients, although further studies are definitely needed (13).

Difficulties in phenotyping CLAD

It is well-known that up to 60% of double lung transplant patients do not have a normal best spirometry after lung transplantation, which may be due to several reasons: diaphragm paralysis/paresis, suture

stenosis, smoking donor, or other causes. When the best postoperative FEV_1 after double LTx remains below 80% predicted, this is called baseline allograft dysfunction (BLAD), with primary graft dysfunction being an important risk factor (14). It is important to point out that there currently is no ISHLT consensus definition. BLAD can be accompanied by an obstructive but also by a restrictive spirometry, making interpretation of CLAD phenotypes even more difficult. That is why it is advised not to use the spirometry at CLAD diagnosis alone, but rather the evolution of the spirometry from best to CLAD, to further phenotype the patient (15). This is exactly one of the reasons why there are so many so-called undefined and unclassified CLAD patients, meaning that some patients may have obstruction and persistent opacities without a TLC decline or a restrictive spirometry without persistent opacities, etc… (15). The same holds true for patients that underwent a single LTx. They usually do not present with a normal spirometry when they reach their best FEV_1 values, so a decline is difficult to interpret as either obstructive or restrictive if they already start from obstruction or restriction ab initio. This is also illustrated in the study by Berra et al., clearly showing that after single LTx, there was only a moderate interobserver agreement for CLAD diagnosis (Kappa 0.69) and a poor interobserver agreement for phenotype adjudication (Kappa 0.52). In this study, 28.3% of CLAD patients remained unclassified, although the presence of RAS like opacities was a strong predictor of death or re-transplantation, regardless of the final phenotype (16), suggesting again that chest CT scan is of utmost importance in prognostication.

Risk factors in BAL and tissue

While long-term risk factors for CLAD have been investigated, it now seems very important to investigate phenotype-specific risk factors. One of the main sources to investigate risk factors is lung tissue providing a unique (usually repetitive) way to investigate the state of the organ. Routine assessment of these biopsies by experienced pathologists can already reveal important risk factors for CLAD. A recent multicenter study confirmed that late-onset (>90 days post-transplant) acute lung injury/organizing pneumonia but not early-onset leads to a two- to three-fold increased risk for CLAD

(17). Next to expert pathologic assessment, novel technologies that have emerged over the last years have also provided innovative ways to analyze tissue fragments and retrieve important information. Shorter tissue telomere length assessed on an endobronchial biopsy taken as soon as 2-4 weeks post-transplantation was found to be predictive for subsequent CLAD. Interestingly, the same study also showed that shorter airway epithelial telomere length was associated with primary graft dysfunction representing a mechanistic link between primary graft dysfunction and CLAD (18). Gene expression microarray analysis of 896 transbronchial biopsies revealed a NK cell-enriched molecular rejection-like state, a T cell-mediated rejection /mixed state and no rejection. Only a T-cell mediated rejection/mixed state was associated with CLAD, while NK cell-enriched molecular state was not (19). Along these lines, a gene expression microarray comparison between mucosal biopsies at the 3rd generation of airway branching and transbronchial biopsies was performed, which revealed that there is a diffuse molecular injury signature that impacts prognosis indicating that both have their value in assessing CLAD risk in LTx (20).

In addition to biopsies, a lot of lung transplant centers also retrieve broncho-alveolar lavage (BAL) on a routine basis that can also be leveraged to assess increases in cellularity and changes in protein and cytokine concentrations. A multicenter study demonstrated that elevated (≥1%) BAL eosinophils significantly and independently increased the risk for definite CLAD development. An elevated BAL eosinophilia was mostly found in conjunction with acute rejection, fungal infection and non-rejection lung injury (21). Quantification of CD16+ NK cells (potentially important in the recognition of DSA's) in 508 lavage samples showed an increased frequency with increasing HLA mismatches and increased AMR grade and reduced CLAD-free survival thereby alluding to its role in pulmonary AMR/CLAD (22). Reduced BAL Club cell secretory protein produced by goblet cells was also found to be a valid measure for early post-transplant risk stratification as it was found to be lower with histological signs of injury and independently associated with probable CLAD (23). Further assessment of markers of epithelial cell death and mucus production in BAL also showed their differential expression in CLAD patients and showed that these can help in differentiating CLAD phenotypes and outcomes (24).

Clinical risk factors

An important determinant of a long-term beneficial post-transplant outcome is undoubtably the degree of HLA mismatch with an increased number of Human Leucocyte Antigen (HLA) mismatches leading to higher risk of graft failure. Reducing the level of HLA mismatching, in either T- or B-cell epitopes, electrostatic differences or amino acid was shown to improve outcomes following LTx as HLA-DRB1345 matching was associated with freedom from RAS and HLA-DQ matching was associated with reduced donor-specific antibody (DSA) development and therefore indirectly also reduced CLAD development (25). This was specifically confirmed for high-risk epitope mismatch found in DQA1∗05 + DQB1∗02/DQB1∗03:01 which was associated with DSA and CLAD development (26).

CLAD management

The management of CLAD remains troublesome and currently there is no definitive treatment to reduce the relentless pulmonary function decline. Therefore, it remains of utmost importance to prevent CLAD development. An open-label, multicentre, randomised, controlled trial compared once daily tacrolimus with twice daily cyclosporin and found that the incidence of CLAD was significantly lower in the once daily tacrolimus versus the cyclosporin group thereby providing strong evidence that tacrolimus should be the first line calcineurin inhibitor in LTx (27).

However, still a significant proportion of patients develop CLAD and novel options to prevent CLAD are warranted. In a single-center study, renin-angiotensin-aldosterone system inhibitors were given to 35 lung transplant patients. This study showed that the treatment was well tolerated but could not demonstrate evidence to influence the incidence of CLAD (28). Next to preventive treatment, it is also important to treat underlying risk factors for CLAD development such as acute rejection and DSA development. Indeed early targeted treatment for DSA in the absence of clinical signs and symptoms of antibody-mediated rejection (AMR), significantly increased CLAD-free and overall survival (29). In that aspect, it is important to note that a randomized placebo controlled trial with de novo belatacept-

based immunosuppression, aiming to reduce DSA development had to stop recruiting earlier because of an increased mortality. In the treated patients, no difference in CLAD development was found between belatacept-treated patients and controls (30).

Once CLAD has been diagnosed, it seems important to perform rigorous phenotyping to assess treatment response and predict survival, as outlined above. Extracorporeal photopheresis (ECP), while not available at every center, seems to have a beneficial effect in patients with established CLAD. A recent study demonstrated that timely intervention is very important as lower baseline pulmonary function led to poorer outcomes following treatment initiation. Interestingly the response to ECP treatment was more uniform than previously thought (31). Another such treatment that is already used for longer times is total lymphoid irradiation (TLI), which was demonstrated to attenuate the pulmonary function decline and seemed to be efficient in both BOS and RAS (32).

Conclusion

CLAD remains the most important complication after LTx, with increased morbidity, a decrease in quality of life and a high mortality (33). Phenotyping of CLAD is essential, as it will reflect the ultimate prognosis after diagnosis. Using spirometry in conjunction with measurements of TLC and a chest CT scan will allow correct phenotyping in a lot of patients, but the spirometric evolution from postoperative best to CLAD needs to be taken into consideration.

Several risk factors have been identified, with some preventable and others not. Strict spirometric follow-up is necessary and immediate investigation is warranted whenever the FEV_1 declines with 10% or more from baseline. Treatment remains difficult, and is becoming more and more phenotype dependent. RAS carries the worst prognosis and in very selected patients, retransplantation seems the only possible treatment that may restore quality of life and prolonge survival of the patient.

Key points

- Novel methodologies to assess pulmonary function and radiologic examination are gradually being implemented in CLAD follow-up

- Tissue and BAL analysis is revealing novel promising biomarkers

- Therapeutic management of CLAD remains troublesome with no definitive treatment.

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